Targeting cancer cachexia: we’re on the way

Temel and colleagues report on the results of two phase 3 trials (ROMANA 1 and ROMANA 2) assessing the effects of anamorelin, a ghrelin-receptor agonist, on cancer cachexia in patients with advanced non-small-cell lung cancer receiving chemotherapy, radiotherapy, or both. The population was of a substantial size, and thus quite well representative of patients with non-small-cell lung cancer, with almost 978 participants enrolled and randomly assigned 2:1 to receive 100 mg of anamorelin or placebo once daily for 12 weeks.

Anamorelin treatment significantly improved lean body mass (as assessed by dual energy X-ray absorptiometry), bodyweight, and anorexia-cachexia-related symptom burden. However, handgrip strength, a measure of muscle function and a co-primary endpoint of the study, did not significantly improve in the anamorelin group. Post-hoc analysis showed that patients treated with anamorelin also had improved body fat mass and appendicular lean body mass compared with those receiving placebo.

Although the findings of Temel and colleagues investigation did not meet one of the primary endpoints (handgrip strength) the study nonetheless provides a significant contribution to the literature on this topic and represents another piece of the puzzle of cachexia prevention and treatment.

Cachexia is a complex and multifactorial disorder characterised by pathophysiological changes that alter body composition, quality of life, performance status, morbidity, and mortality, with up to half of patients with cancer dying with cachexia and up to 20% of them having cachexia as the cause of death. In view of its increased prevalence, cachexia has been proposed to be a cancer comorbidity. Although substantial progress on the pathogenic mechanisms, definition, and classification of cachexia has been achieved, such advancements have not yet translated into effective strategies that can prevent or treat this devastating disorder. It is becoming increasingly clear that multimodal strategies, encompassing drugs, physical activity, and optimum nutritional support are required. The finding that anamorelin might attenuate the loss of muscle mass (sarcopenia), or even improve lean body mass during antineoplastic treatments might have major implications in clinical practice. Sarcopenia in cancer adversely affects survival and increases dose-limiting chemotherapy toxic effect, causing dose reduction or even treatment interruption. Skeletal muscle is the most abundant tissue in the body and, besides contraction, it accomplishes many metabolic functions, such as modulation of insulin resistance, energy expenditure, and secretion of peptides regulating anabolism and catabolism, etc. Therefore, muscle depletion occurring in cancer and in other chronic diseases should not longer be seen as a simple determinant of mechanical function loss, but rather as a major cause of whole-body metabolic impairment, in turn responsible for negative outcomes. Strategies capable of maintaining or improving muscle mass during cancer treatment could prove beneficial even if they are not associated with a measurable improvement in mechanical function, particularly when considering that the relationship between muscle mass and contractile function is highly variable. In this respect, adequate nutritional support aimed at satisfying protein and caloric needs of patients with cancer plays a prominent part, especially if we consider that on the one hand, nutrient intake in patients with cancer is largely suboptimum, but on the other, the anabolic potential of nutrients is maintained even in advanced stages of cancer, which strengthens the view that effective nutritional strategies should be implemented concomitantly to cancer treatments as a part of a multimodal approach. Temel and colleagues reported improvements in anorexia scores during anamorelin treatment, a finding that, coupled with improvement in bodyweight and composition, would argue in favour of a positive effect of anamorelin on food intake. However, the authors did not measure actual food intake in their patients, which makes it difficult to ascertain whether improvement in anorexia translated into optimum nutritional intake, capable of effectively sustaining the anabolic boost of anamorelin. We cannot exclude that the gain in lean body mass and body weight would have been even more evident in appropriately nourished patients. Physical exercise is deemed safe and effective for the prevention of muscle loss and dysfunction of chronic diseases. However, evidence is insufficient to determine safety and effectiveness of exercise.
programmes in cancer cachexia. Moreover, exercise programmes are frequently difficult to implement because of fatigue, anaemia, and comorbidities.

In conclusion, the ROMANA 1 and ROMANA 2 trials offer new hopes for more effective therapeutic strategies for cancer cachexia, where the anabolic properties of drugs, exercise, and optimum nutrition should be integrated to produce measurable effects on patients’ quality of life and clinical outcomes.

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